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Desert-dust exposure is associated with increased risk of asthma hospitalization in children

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At A Glance Commentary

Scientific Knowledge on the Subject

Desert dust particles, including quartz, that cause inflammatory responses in the airway in animal studies, are transported to wide-spread regions around the globe. However, no studies have investigated the magnitude of desert-dust effects on asthma exacerbation with quantitative objective measure of desert-dust in the air, taking into consideration the effect of other air pollutants.

What This Study Adds to the Field

Desert-dust exposure was associated with the increased risk of asthma hospitalization for asthmatic children. The risk was particularly high for boys.

Abstract

Rationale: Desert dust particles, which include quartz that cause inflammatory responses in the airway in animal studies, are transported to wide-spread regions around the globe. Epidemiologically, areas impacted by desert-dust storms, such as communities in the Middle East and the Caribbean, seem to have higher incidences of asthma than might be expected. We investigated the magnitude of association between airborne mineral-dust concentration and hospitalization of children for asthma exacerbation by using Light Detection And Ranging (LIDAR) with a polarization analyzer for an exposure measurement, which can distinguish mineral-dust particles from other particles.

Methods: A case-crossover design was used. The exposure measurement was LIDAR's non-spherical extinction-coefficient. The outcome measurement was hospitalization of children ages 1-15 years for asthma exacerbation in eight principal hospitals in Toyama, a local area in Japan, facing to Japan Sea, during February to April, in 2005-2009.

Findings: During the study period, there were 620 admissions for asthma exacerbation, and 6 days with a heavy dust event (daily mineral-dust concentration above $0.1\text{mg}/\text{m}^3$). Conditional logistic regression showed a statistically significant association between asthma hospitalization and a heavy dust event. The crude odds ratio of the heavy dust event for

hospitalization on the day was 1.88 (95%CI: 1.04-3.41; $p=0.037$), and the odds ratio of heavy dust event during the previous week was 1.83 (95%CI: 1.31-2.56; $p=0.00043$). The odds ratio adjusted by other air pollutant levels, pollen, and meteorological factors was 1.71 (95%CI: 1.18-2.48; $p=0.0050$).

Interpretation: Heavy dust events are associated with an increased risk of asthmatic hospitalizations.

Asian dust, Kosa, mineral dust, African dust, quartz

(249 words)

Introduction

Aerosol particles are produced by a variety of processes, both natural and anthropogenic. Among them, desert dust constitutes about 40% of the aerosol mass injected into the troposphere (1).

Quartz, an amorphous and crystalline silica, included in dust sand, is known to cause respiratory disease in occupationally exposed people, and highly exposed people who live close to deserts (2-5). It causes inflammatory responses with the release of inflammatory cytokines in the lungs of rats in experimental studies (6-8).

Desert dust is transported to wide regions of the world. Dust originating from the Sahara desert can be transported across the Atlantic Ocean, and reaching northeastern South America, the Caribbean, Central America, and southeastern United States (9). Dust originating from the Taklimakan desert was transported more than one full circle around the globe in about 13 days (10). Epidemiologically, areas impacted by desert-dust storms, such as communities in the Middle East and the Caribbean, seem to have higher incidences of asthma than might be expected (2,11-13). Although several clinical studies tried to relate desert dust to asthma, none had a quantitative objective measure of desert dust in the air (14-19) except one that measured the amount of some minerals in the air (20). On the other hand, extensive studies of the atmospheric aerosol particle load in the troposphere have been conducted in the last decades using the Light Detection and Ranging

(LIDAR) technique in North America, Western Europe, and in Asia (10,21-27).

LIDAR is an optical remote sensing technology that measures properties of scattered light to find range and/or other information on a distant target. The LIDAR system with a polarization analyzer can distinguish mineral-dust particles (non-spherical particles) from non-mineral-dust particles (spherical particles) (28-32). While PM_{2.5} and PM₁₀ differentiate the size of particles but do not differentiate mineral-dust from non-mineral dust, the LIDAR system with a polarization analyzer does not differentiate the size of particles but does differentiate the shape of particles. Thus, the LIDAR system can specifically measure quantity of mineral dust. In Asia, observations of tropospheric aerosol particles are continuously being conducted using a network of LIDARs at 23 locations in Japan, Korea, and China.

The present study took place in Toyama, Japan; a local prefecture occasionally susceptible to Asian dust events in the spring. Asian dust is a wind-blown dust originating from the deserts of Mongolia and China. It is a seasonal event, and Asian cities experience yellowish air on several days in the spring when the dust is blowing. We investigated the magnitude of the effect of mineral-dust particles on children's asthma exacerbation using the LIDAR measurement. The primary hypothesis was that heavy dust events are associated with an increased risk of asthmatic hospitalizations.

Methods

Study design

The present study used a case-crossover design (33-35). Four controls were matched to each hospitalization, ± 2 weeks and ± 4 weeks. The study-protocol was approved by the Human Research Protection Program of the University of California, San Diego.

Hospitalization data

Data were obtained from the hospitalization records of eight principal hospitals in Toyama, Japan. Potential cases were children aged 1-15 years, who had at least one hospitalization with the admission diagnosis of asthma in any of the eight principal hospitals in Toyama between February and April, from 2005 to 2009. 'Hospitalization' referred to actual inpatient admission, and did not include emergency visits that did not end in admission.

Dust, air pollution, and meteorological data

The mineral-dust data were based on measurement by the LIDAR system with a polarization analyzer (10,36,37).

A heavy-dust-event day *a priori* was defined as the day when the daily (24-hour) average dust extinction coefficient in Toyama, measured by LIDAR

under 1km height from the ground, recorded more than 0.1 /km, which corresponded to 0.1 mg/m³ mineral-dust particles, the standard threshold for particulate matter (36,37).

Statistical Analysis

Initially, a conditional logistic regression analysis was performed using hospitalization as the dependent variable, and heavy-dust-event as the independent variable changing the hazard/control period from one to seven days to determine the crude odds ratio (OR) of heavy-dust-events for asthma hospitalization. We examined possible climatic confounders (daily average temperature, temperature difference from the previous day, temperature difference within the day, air pressure, air pressure difference from the previous day, humidity, and wind speed) if each had an increased OR for asthma hospitalization with various cut-off value and various lag-structures up to lag 0-6 (days 0 to 6). Then we performed cross-correlations of the variables, and conducted a conditional logistic regression to determine the climatically adjusted OR using hospitalization as the dependent variable and, as independent variables, heavy-dust event and all climatic variables that showed apparent increase ($p < 0.1$) of OR for asthma hospitalization among above. We examined other air pollutants (gaseous NO₂, SO₂, and O₃, non-mineral-dust particles, and pollen) if each had an increased OR for asthma hospitalization with various cut-off values and various lag-structures up to

lag 0-6 (days 0 to 6). Then these other air pollutants were each examined by a two-compartment model approach to determine if they had an effect on the OR of heavy-dust event to asthma hospitalization. Finally we conducted a conditional logistic regression to obtain the best-fit OR using heavy-dust event, the climatic variables described above, and other air pollutants described above, as independent variables.

The same conditional logistic regression analysis was conducted on each subgroup of sex and age defined *a priori* (ages 1-5 years, 6-12 years, 13-15 years). We also conducted the same conditional logistic regression using a heavy-dust event defined by a more conventional method, suspended particulate matter (SPM; daily average particulate matter level 0.1 mg/m³ or above), as an exposure measurement.

R version 2.9.2 was used for statistical analysis.

Additional detail on the method for making these measurements is provided in an online data supplement.

Results

Subjects

During the study period, there were a total of 620 initial hospitalizations for asthma in children who were 1 to 15 years of age. The hospitalization characteristics are described in Table 1. There were more male than female paediatric asthma admissions, consistent with previously published global and regional reports (38). Half of the admissions were for ages 2-5 years. Admissions were most frequent in the month of April, and in 2006.

Mineral-dust levels and other air pollutant levels

Daily average mineral-dust levels above $0.1\text{mg}/\text{m}^3$ were recorded on 6 days in Toyama during the study period (Figure1). Other air pollutant levels and meteorological observations during the study period are shown in Table 2. Correlations between mineral dust levels and air pollutants or meteorological variables are presented in Table E1 (see Table E1 in the online data). There were no particularly strong correlations among them. In the local area during the study period, cedar was the major source of pollen, and cypress pollen was also observed in a lesser amount.

Relationship between heavy mineral-dust exposure and asthma hospitalization

Figure 2 shows the crude ORs for the relationship between asthma hospitalizations and a heavy-dust-event on the day of the admission (lag 0) and on the previous cumulative 1-7 days (lag 0-1 to lag 0-7). A statistically significant association was shown between asthma hospitalization and a heavy dust event. The crude odds ratio of the heavy dust event for hospitalization on the day was 1.88 (95%CI: 1.04-3.41; $p=0.037$). The positive association was maintained regardless of the hazard period studied. The crude OR of heavy-dust-event on any day during the previous week (lag 0-6) was 1.83 (95%CI: 1.31-2.56; $p=0.00043$).

A crude association between climatic observations and asthma hospitalization is shown in Table E2 (see Table E2 in the online data). Asthma hospitalization had apparent associations ($p<0.1$) with average temperature, air pressure difference from the previous day, and humidity. We conducted a conditional logistic regression with hospitalization as the dependent variable, and, as independent variables, heavy-dust-event and climatic variables with apparent association for asthma hospitalization described above, and we obtained the climatically adjusted OR of 1.86 (95% CI: 1.32-2.62, $p=0.00037$) for heavy-dust-event during the previous week.

Table 3 shows the OR and climatically adjusted OR for the heavy-dust event (lag 0-6) taking into consideration one of the other pollutants (two-pollutant model). For each two-pollutant model, we examined various models with various lag-structures from 0 to 0-6 days, and various cut-off levels, but the

single-pollutant effect of heavy-dust-event was only slightly attenuated by other pollutants and remained significant after adjustment in all models. Table 3 shows the OR of heavy-dust events for asthma hospitalization in the two-pollutant model using results from a model that showed the strongest association with asthma hospitalization for each other pollutant. The final model for obtaining the adjusted OR of heavy-dust event for asthma hospitalization was determined to be the one with the climatic variables and other pollutant variables described above. The best-fit OR of heavy-dust event for asthma hospitalization was 1.71 (95%CI: 1.18-2.48; p=0.0050).

We also conducted the same conditional logistic regression using a heavy-dust event defined by SPM as an exposure measurement, and a statistically significantly increased OR was shown using this method (see Figure E4 in the online data).

Figure 3 presents the crude odds ratio of heavy-dust-event for asthma hospitalizations in each sex group and sub-group defined *a priori* (ages 1-5 years, 6-12 years, and 13-15 years). The associations were particularly strong for boys. And the risk for hospitalization on the day of heavy-dust-event was particularly high for boys (OR: 2.32, 95% CI: 1.10-4.87) and for elementary school ages (OR: 3.33, 95% CI: 1.02-10.92), while the risk for hospitalizations following the week seemed similar among the sub-groups.

Discussion

In this study, heavy mineral-dust exposure was significantly associated with an increased risk of asthma hospitalization in children. Although we presumed in the study protocol that a high association would be observed during three days following mineral-dust exposure, a high association was maintained even after four to six days after the exposure. This is, as far as we know, the first report that showed a clear association between mineral-dust exposure and increased risk of asthma hospitalization. Previously reported efforts to investigate the association between desert-dust exposure and asthma exacerbation included two studies in the Caribbean islands on Sahara dust, one in Australia on local dust, and one in Taiwan and three in Korea on Asian dust (15-20). All but Korean studies showed subtle linkage, or did not show obvious associations with visits or admissions for asthma. The studies from Korea showed a significant decrease in peak-flow for asthmatic children and adults on Asian-dust days, although a quantitative definition of Asian-dust days was not presented in the reports, and effects of other air pollutants were not taken into consideration (17,19,20). In all these studies, there were some days that had particulate matter above 0.1 mg/m^3 during the study periods. Possible explanations for the variety of results would be difference in exposure-measurement, study design, and the general knowledge of people about the risk of dust, and local variation of size, chemical, mineralogical and microbiological composition of dust particles.

The size distribution of Asian dust particles being lifted into the air and carried to Japan had a peak of 4 μ m, and ranged mostly from 0.5-10 μ m in diameter. Particles this size can penetrate into the lower respiratory system and particles under 2.5 μ m in diameter can enter gas-exchange region of the lung (2).

Asian dust contains quartz as the main component (6). Quartz, an amorphous and crystalline silica, has been reported to cause inflammatory responses with the release of inflammatory cytokines in the lungs of rats (7,8,39). Furthermore, Asian dust contains various chemical compounds including sulfate (SO_4^{2-}) or nitrate (NO_3^-) derived from alkaline soil, which capture acidic gases, such as sulfur oxides (SO_2) and nitrogen oxides (NO_2), during its transportation (40). Hiyoshi reported that Asian dust and ovalbumin administered into mice demonstrated an enhanced adjuvant effect of sand dust on ovalbumin-specific IgG1 production, when administered together with sulfate (41).

Another important constituent is organics, such as bacteria, fungi, virus, and other microorganisms. During Asian dust events in Taejon, Korea, the bacterial CFU concentration increased on average 4.3 times over that observed under normal atmospheric conditions (42). Griffin reported that Asian dust included the known allergenic fungi (2). Dust-borne microorganisms in particular can directly impact the immune system of individuals sensitive to those agents, and lipopolysaccharide or beta-glucan

included in the micro-organisms are known pattern-associated molecular patterns (PAMPs) that activate dendritic cells to mount an immune response (43). A study by Ichinose demonstrated that inhalation of dust sand from Tengger Desert (China), which had higher amounts of beta-glucan than dust from the Maowusu Desert (Inner Mongolia), caused greater eosinophil infiltration in the murine airway than did dust from the Maowusu Desert (44). Another study further showed that the heated desert sand, in which microbiological materials and sulfate were excluded by heating, had less effect on allergic lung inflammation (45). Accordingly, quartz, sulfate, and microbiological materials would be included in the pathogenicity of desert sand.

The measured quartz content in a major dust storm is very similar between Asian dust and African dust (60.95% in North Africa, and 60.26% in China), and the concentrations of culturable bacteria and fungi and fungal spores in dust storms are greatly elevated relative to background in most investigated places (2,46). Accordingly, it is quite possible that not only in East Asia, but also in many other areas where wind-borne desert dust is observed, desert dust exposure greatly contributes to asthma admissions of children.

In our study, there were no heavy-dust-event days in 2005 yet 25% of the hospitalizations occurred in that year. There was a downward trend in hospitalizations from 2007-2009 compared with 2006 yet there were three heavy-dust-event days during this period. Although the desert dust exposure

was shown as an independent risk for asthma hospitalization in this study, the contribution of heavy-dust events to the total number of asthma hospitalization may be limited in Japan. This is reasonable considering that the heavy-dust event occurred only on 6 days of the 446 days of the study period. The heavy-dust events may be a more substantial contributor to the total number of asthma hospitalizations in some other parts of the world where dust events occur more frequently than in Japan.

It is not only desert dust that exacerbates asthma control, but infections, irritants such as tobacco smoke, and other pollutants are also known to exacerbate it. In our study, other than heavy dust events, we found statistically significant associations with asthma hospitalization in gaseous NO_2 , gaseous SO_2 , gaseous O_3 , non-mineral particles, and pollen in some cut-off levels in some lag-periods. Similarly, we observed an increased OR when using particulate matter count for an exposure measurement though this method does not clearly differentiate mineral dust from other particles. Thus, using LIDAR system, it would be possible to caution asthmatic children to avoid exposure to heavy dust environment.

In the present study, the risk of mineral dust for asthma hospitalization was particularly high for boys (Figure 3A). Especially, the risk on the first day of the exposure was high for boys and for elementary school ages (6-12 years old), while girls and infants (1-5 years old) showed the increased risk later in the week (Figure 3B). The percentage of elementary school ages among all

ages in boys (14%) was lower than in girls (26%). Accordingly the stronger association observed in boys cannot be explained by the distribution of ages. It is interesting that boys showed a higher OR in heavy-dust event while girls showed a higher OR for other air pollutants such as NO₂, SO₂, and Ox in our study. The high risk on the first day observed in boys and in elementary school age may have been influenced by any of several factors: length of exposure to outdoor air; exercise in outdoor air; or any immune mechanism which might make these groups more susceptible to mineral-dust particles. Further investigations should be conducted to investigate if there are any difference in pathogenesis between the earlier asthma symptom and later one, and to determine if there are especially susceptible subpopulations among asthma patients including adults.

Aerosolized particles have various effects on the atmospheric environment, including chemical and radiative effects, and also on the oceanic environment (2). It is not realistic to eliminate the dust events, which would negatively influence living creatures in various ways. However, we believe that we can at least minimize the detrimental effects of desert-dust exposure by giving information to relevant people, so that susceptible children can protect themselves.

Our study has following limitations. First, the interpretation was limited by the occurrence of only six heavy-dust-event days in the study period. Second, the exposure data were not individually based, but were based on

measurements in the locality. Accordingly, it is possible that we underestimated the association because of mis-categorizations. Third, because we chose hospitalizations for the outcome measure, the study results are generalized only to children who can be hospitalized. However, an observational study in Japan shows that 17.5% of intermittent mild asthma paediatrics also experience hospitalization, and accordingly our study result will probably be applicable not only for moderate to severe patients but also for mild patients (47). Lastly, the associations we found were only for acute effects. Chronic effects should be further investigated.

As for the strength of our study, we used objective measures for both exposure and outcome, so that recall bias or presentation bias could be excluded. Additionally, we used the LIDAR non-spherical extinction coefficient for an exposure measure, so that we could focus on the effect of mineral-dust particles.

In conclusion, this study suggested that heavy dust events were significantly associated with the increased risk of asthma admission for asthmatic children. Physicians, patients, and the general public, including schools and pre-schools, should be adequately informed of the health implications of heavy desert dust exposure so that those at risk can minimize the deleterious effects.

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FIGURE LEGENDS

Figure 1. Daily levels of mineral-dust particles (non-spherical particles) and non-mineral-dust particles (spherical particles) during the study period

Red represents mineral dust level, and blue represents non-mineral dust level. Arrows represent the days with more than 0.1 mg/m³ mineral dust particle levels.

Figure 2. Crude odds ratios for the relationship between asthma hospitalizations and heavy mineral dust exposure (daily average level above 0.1mg/m³) on the day of the admission (lag 0) or the previous 1-7 days (lag 0-1 to lag 0-7)

Error bars represent 95% CIs.

Figure 3. Crude odds ratios of heavy mineral dust exposure (daily average level above 0.1 mg/m³) for asthma hospitalizations on the day of the admission (lag0) or the previous 1-7 days (lag 0-1 to lag 0-7) in each subgroup

Figure 3A for girls (n=253) and boys (n=367), **Figure 3B** for aged 1-5 years (n=495) and aged 6-12 years (n=117).

Error bars represent 95% CIs.

Table1 Characteristics of cases

Number (%)				Number (%)	
Sex				Month	
Male	367 (59)			Feb	175 (28)
Female	253 (41)			Mar	199 (32)
Total	620 (100)			Apr	246 (40)
				Total	620 (100)
Age (years)	Male	Female	All	Year	
1	133	52	185 (30)	2005	151 (24)
2-5	178	132	310 (50)	2006	170 (27)
6-12	52	65	117 (19)	2007	90 (14)
13-15	4	4	8 (1)	2008	118 (19)
Total	367	253	620 (100)	2009	91 (15)
Mean	3.2	4.2	3.6	Total	620 (100)
Median	2	3	2		

Table 2 Frequency distribution of the daily levels for air pollutants and meteorological observations during the study period

	Days	Mean	SD	25thP	Med	75thP
Mineral dust particles ($\mu\text{g}/\text{m}^3$)	400	21.27	25.66	7.82	15	25.08
Non-mineral-dust particles ($\mu\text{g}/\text{m}^3$)	446	28.05	20.55	4.64	22.87	35.77
Suspended particulate matter ($\mu\text{g}/\text{m}^3$)	446	17.52	11.68	9	14	23
NO ₂ (ppm)	446	12.61	5.85	8	12	17
SO ₂ (ppm)	446	0.86	0.69	0	1	1
Ox (ppm)	446	35.17	9.79	29	36	41
Pollen (/cm ²)	400	31.8	76.7	0	3	21
Average temperature (°C)	446	7.64	4.86	3.8	7.2	11.2
Temperature difference from the previous day (°C)	446	0.15	2.93	-1.4	0.3	1.8
Temperature difference within the day (°C)	446	9.13	3.71	6.2	8.8	11.2
Average air pressure (hPa)	446	1014.7	6.34	1010.1	1015.2	1019.5
Air pressure difference from the previous day (hPa)	446	-0.01	0.29	-3.90	0.55	4.20
Wind speed (m/s)	446	6.7	2.59	4.6	6.2	8.375
Humidity (%)	446	74.4	12.4	66	76	84

Table 3 Odds ratio of heavy-dust-events for asthma hospitalization adjusted by other pollutants in two-pollutant model

	Single-pollutant model	Two-pollutant model adjusted by				
		Non-M-dust	Pollen	NO ₂	SO ₂	Ox
Crude OR	1.83	1.79	2.04	1.70	1.80	1.63
(95% CI)	(1.31-2.56)	(1.28 - 2.51)	(1.44 - 2.88)	(1.21 - 2.39)	(1.28 - 2.55)	(1.15 - 2.29)
Climatically adjusted OR	1.86	1.83	2.19	1.76	1.86	1.66
(95% CI)	(1.32-2.62)	(1.30 - 2.58)	(1.50 – 3.04)	(1.25 - 2.48)	(1.31 - 2.64)	(1.17 - 2.35)

Definition of abbreviations: Non-M-dust = non-mineral-dust particles, OR = odds ratio, CI = confidence interval

Non-M-dust (on the day: lag 0 day) and pollen (on the previous day: lag 1 day) was treated as a five level variable, NO₂ was treated as dichotomous (with cut-off value of 80 percentile, and cumulative lag 0-5 days), and SO₂ (on the day: lag 0 day) was treated as a five level nominal variable.

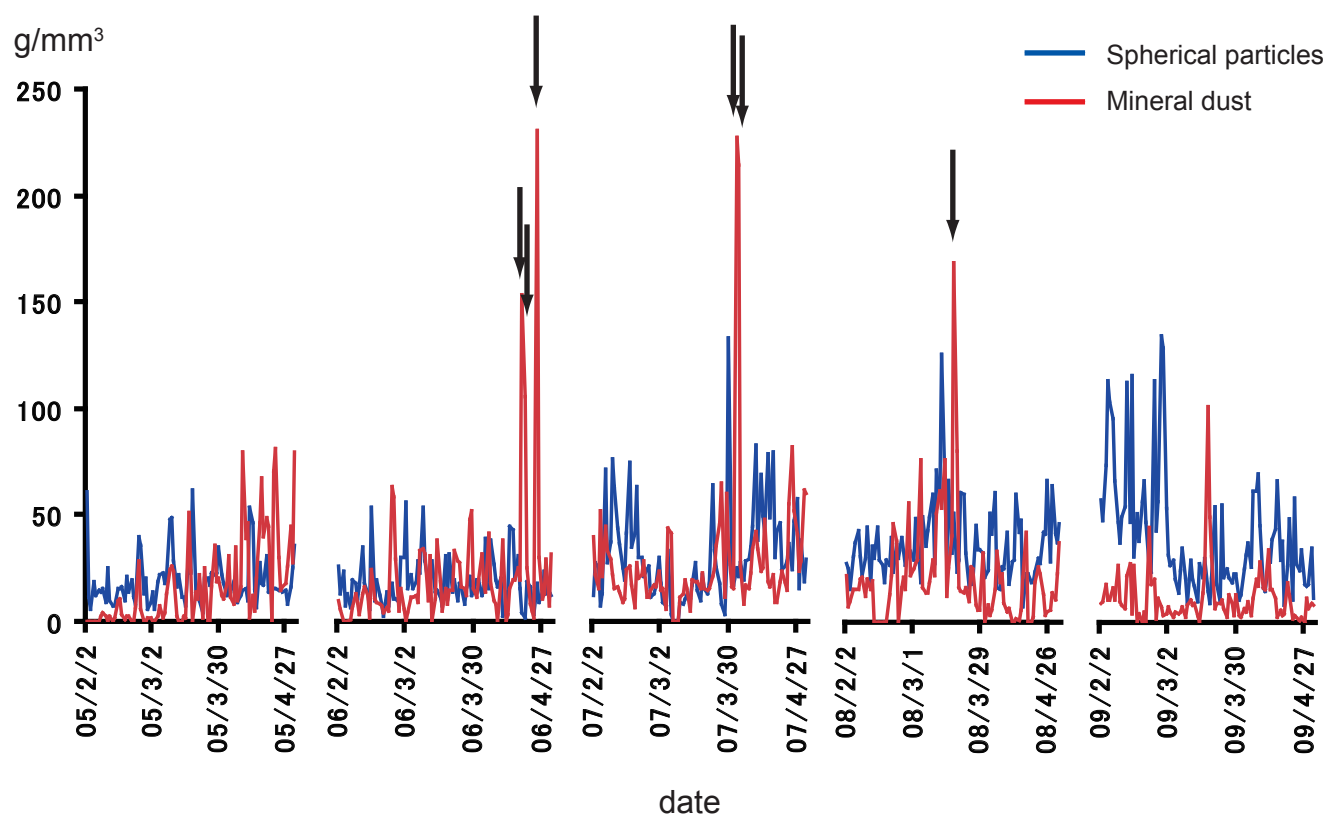


Figure 1

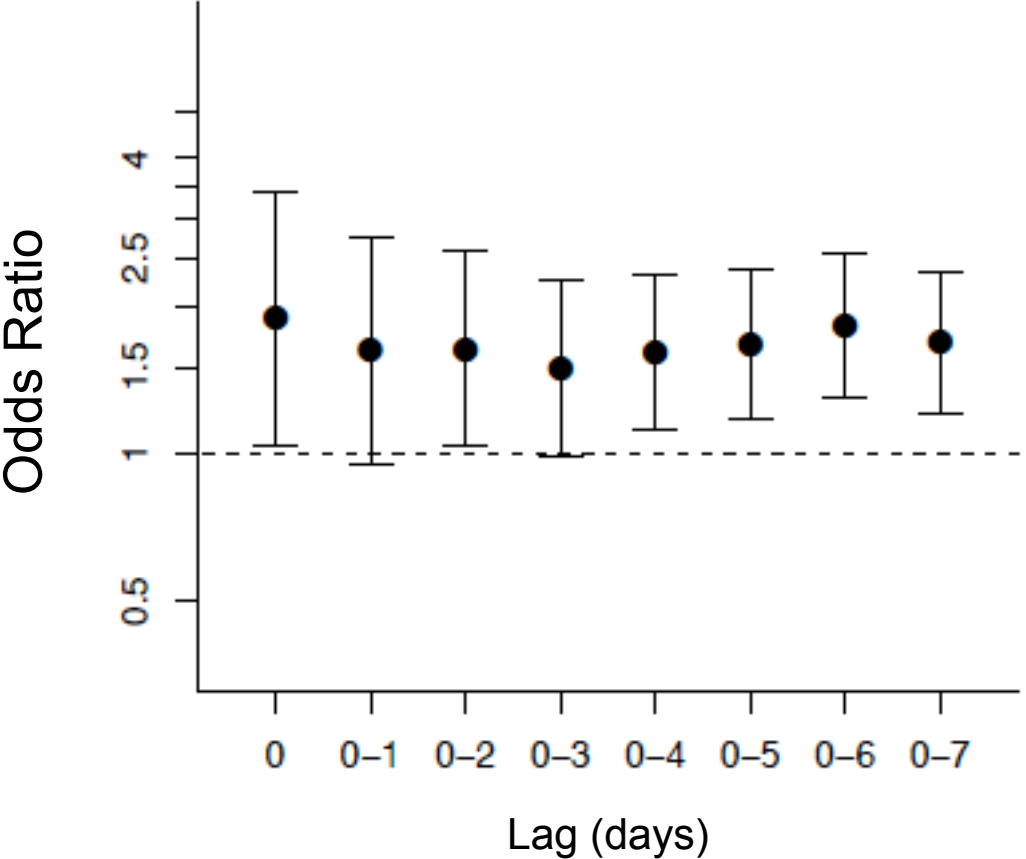


Figure 2

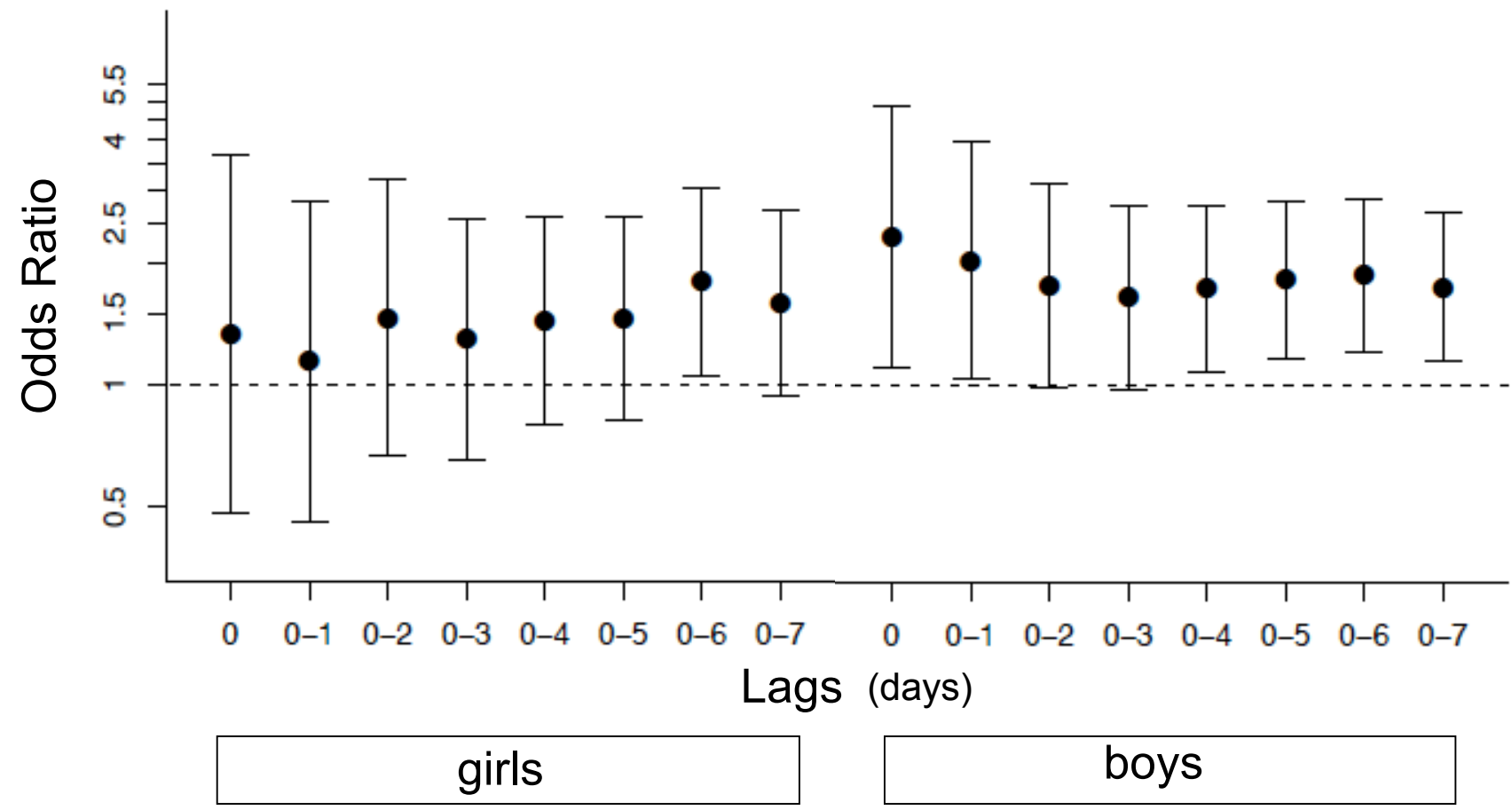


Figure 3A

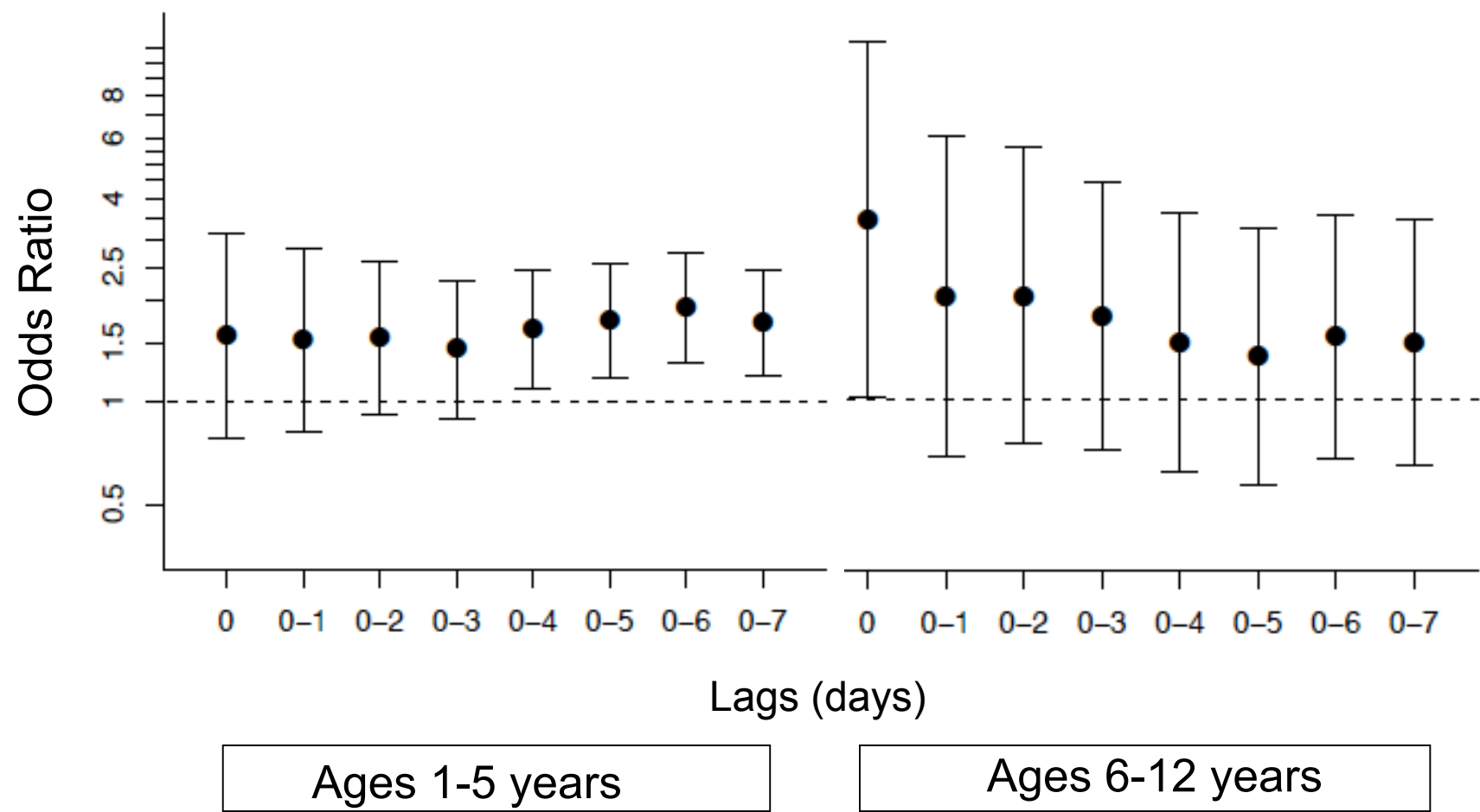


Figure 3B

Desert-dust exposure is associated with increased risk of asthma hospitalization in children

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Online Data Supplement

Methods

Study design

The present study used a case-crossover design, which is an analytic technique designed to assess the effect of transient exposure on the risk of acute illness, and has been increasingly used in epidemiological studies investigating acute effects of ambient air pollution (E1). In this design, the exposure frequency during a time window immediately before the illness onset (hazard period) is compared with the exposure frequency during control periods when no illness followed. As each case serves as its own referent, the design has the ability to control by design rather than by statistical modeling for potential confounding caused by fixed individual characteristics including measured and unmeasured variables (E2). The case-crossover design is able

to control for time trends in the data through the use of information both before and after the events (E3).

In this study, four controls were matched to each hospitalization, ± 2 weeks and ± 4 weeks. In this approach, day of the week was also controlled by design. When the subjects were in the hospital on the control day, that day was excluded from the control because the patient was not at risk for hospitalization on that day, and a substitute control day was selected from ± 3 weeks or ± 5 weeks. The study protocol was approved by the Human Research Protection Program of the University of California, San Diego.

Setting

The study location was Toyama, Japan; a local prefecture about 50 km in diameter, with a population of about one million, and with no area-specific air pollution problems reported. It is located almost in the middle of Japan, facing the Japan Sea, and surrounded by 3000 m mountains (Figure E1). The usual main constituent of the aerosol particles in this area was reported as non-sea-salt derived SO_4^{2-} and NH_4^+ (E4). Aerosol particles presumably also contained diesel exhaust and other pollutants typically observed usually in urban locations in the study situation.

Toyama is occasionally susceptible to Asian dust events usually in spring, and thereby the study duration was determined as between February and

April each year, from 2005 to 2009, when exposure data (LIDAR data) was available.

Hospitalization data

Data were obtained from the hospitalization records of eight principal hospitals, which are located within 50 km from where the exposure data (LIDAR data) was obtained in Toyama, Japan (Figure E2). Asian dust comes in a large cloud (Figure E1 and E3) that sometimes covers all areas in Western Japan, and therefore we considered that the dust measurements were applicable to patients who were admitted in those hospitals (E5, E6). Potential cases were children aged 1-15 years, who had at least one hospitalization with the admission diagnosis of asthma in any of the eight principal hospitals in Toyama between February and April, from 2005 to 2009. 'Hospitalization' referred to actual inpatient admission, and did not include an emergency visit that did not end in admission. Children <12 months of age or with serious cardiovascular or respiratory diseases other than asthma were excluded, as the diagnosis of asthma in these groups may be un-reliable. We *a priori* defined the first hospitalization of the year as cases, and excluded the subsequent hospitalizations from the analysis because, after initial admission, patients were considered at higher risk for subsequent hospitalization.

Dust, air pollution, and meteorological data

Mineral-dust data and other air pollution data were obtained from The National Institute for Environmental Studies in Japan, and meteorological data were obtained from the Japan Meteorological Agency. The pollen data was obtained from the Japan Weather Association. In the local area during the study period, cedar was the major source of pollen, and cypress pollen was also observed in a lesser amount. The mineral-dust data as well as non-mineral-dust data were based on measurement by the LIDAR system with a polarization analyzer, which distinguishes mineral-dust particles (non-spherical particles) from non-mineral-dust particles (spherical particles); that is, while PM_{2.5} and PM₁₀ differentiate the size of particles but do not differentiate mineral-dust from non-mineral dust (sphere or non-sphere), the LIDAR system does not differentiate the size of particles but does differentiate the shape of particles (E7-E11). Thus, the LIDAR system could specifically measure quantity of mineral dust. Daily (24-hour) average values were obtained for both a non-spherical extinction-coefficient, which was converted into mineral-dust particle mass concentration by a formula, and a spherical extinction coefficient, which was converted into non-mineral-dust particle mass concentration (E12, E13).

A heavy-dust-event day *a priori* was defined as the day when the daily average dust extinction coefficient in Toyama, measured by LIDAR under 1km height from the ground, recorded more than 0.1 /km, which

corresponded to 0.1 mg/m³ mineral-dust particles (E12, E13). This was the standard threshold for particulate matter, and the threshold for a public announcement of Asian dust arrival on the LIDAR homepage run by the Ministry of the Environment in Japan. For the main analysis, exposure status of a patient's hazard/control period was defined as exposed when at least one of the days during the hazard/control period was a heavy-dust-event day, and was defined as un-exposed when neither of the days during the hazard/control period was a heavy-dust-event day.

There were missing values for the non-spherical extinction coefficient on some snowy, foggy, or rainy days. These missing values were treated as 0 /km, which corresponded to 0 mg/m³ in density, taking into account their capturing the particles to the ground, presumably resulting in a very low particulate concentration in the air.

The spherical extinction coefficient and the non-spherical extinction coefficient (/km) were converted to mass concentration (mg/m³) by using the following formulae (E12, 13).

$$\text{Mass concentration (mg/m}^3\text{)} = F * \text{extinction coefficient (/km)}$$

$F = 1000$ (for non-spherical extinction coefficient, that is, for mineral-dust)

$$F = 566 - 6.24 * X + 5.56 e^{-2} * X * X - 4.62 e^{-4} * X * X * X$$

(X=Relative humidity) (for spherical extinction coefficient, that is, for non-mineral-dust)

Gaseous NO₂ was measured by a wet photometric analysis or by a dry chemiluminescence analysis, gaseous SO₂ was measured by a dry ultraviolet absorption analysis, and gaseous Ox was measured by an ultraviolet absorption analysis. Suspended particulate matter (SPM), which was any particle collected with an upper 100% cut-off point of 10 µm aerodynamic diameter, and a 50% cut-off diameter for which is assumed to be approximately 7 µm, that is, PM₇, was measured by a β ray attenuation method and pollen was measured by the Durham method. (E13-E15)

Statistical Analysis

Initially, a conditional logistic regression analysis was performed using hospitalization as the dependent variable and heavy-dust-event (>0.1 mg/m³) as the independent variable (1; heavy dust event on any of the hazard/control period, 0; no heavy-dust-event on any of the hazard/control day) changing the hazard/control period from one to seven days to determine the crude odds ratio (OR) of heavy-dust-events for asthma hospitalization. Possible confounding climatic variables (daily average temperature, temperature difference from the previous day, temperature difference within the day, air pressure, air pressure difference from the previous day, humidity, and wind speed; variables were analyzed as continuous or dichotomous depending on

the distribution of the variable) were examined if each had an increased OR for asthma hospitalization with various cut-off values and various lag-structures up to lag 0-6 (days 0 to 6). Cross-correlations of the variables were examined, and a conditional logistic regression analysis was conducted using outcome as the dependent variable (1; hospitalization, 0; control), and, as independent variables, heavy-dust event on any day during the previous 7 days, (0; no heavy-dust-event on any of the previous 7 days), and climatic variables that showed apparent ($p < 0.1$) increase of OR for asthma hospitalization in the precedent analysis (average temperature, air pressure difference from the previous day, and humidity). Other air pollutants (gaseous NO_2 , gaseous SO_2 , gaseous Ox, non-mineral-dust particle, and pollen; variables were analyzed as five level nominal or dichotomous with various cut-off level; median, 80 percentile, 90 percentile and 95 percentile, and with various lag-structure up to 7 days) were examined if each had an increased OR for asthma hospitalization. The effect of these pollutants on the OR of heavy-dust event for asthma hospitalization was examined with a two-pollutant model approach in all the above models. We also determined the best-fitted model for each pollutant with a cut-off level and a lag-structure that showed the strongest association with asthma hospitalization among all the above models. Finally, we conducted a conditional logistic regression to obtain the best-fit OR using hospitalization as the dependent variable and, as independent variables, heavy-dust event, the climatic variables described

above, and other air pollutants described above with a cut-off value and a lag structure that showed the strongest association with asthma hospitalization for each.

Additionally, we conducted the same conditional logistic regression analysis using particulate matter, which has been conventionally used as an exposure measurement for dust particles and does not differentiate mineral-dust particle from other particles.

The same conditional logistic regression analysis was conducted on each sub-group of sex and age defined *a priori* (ages 1-5 years, 6-12 years, and 13-15 years). A conditional logistic regression analysis was tried in each sub-group using hospitalization as the dependent variable and heavy-dust-event on the day (lag 0) or on the day with various lag-periods (lag 1 to lag 6) as the independent variable, to see when the risk for asthma hospitalization was increased by a heavy-dust-event in each group.

Also examined was how the OR increased in accordance with an increase in cut-off value for the mineral-dust level to examine if lower-level mineral-dust also influenced the asthma hospitalization.

R software (R version 2.9.2 for Windows; R Foundation, www.r-project.org) was used for statistical analysis.

Results

Associations between asthmatic hospitalizations and mineral-dust level with non-cumulative lag structure

Figure E5 shows crude ORs of heavy dust event for asthma hospitalizations on the day of admission (lag 0) or on the day some days before admission (lag 1 to lag 6), that is, by non-cumulative lag-structure. The risk for hospitalization was high on the day of heavy-dust-event (lag 0) and also on 4 to 6 days after the event (lag 4, lag5, and lag 6). In particular, the risk on the first day of the exposure was high for boys and for elementary school ages (6-12 years of age), while girls and infants (1-5 years of age) showed an increased risk later in the week.

Associations between asthmatic hospitalizations and mineral-dust level with various cut-off value

Figure E6 shows how the OR increased in accordance with an increase in cut-off value for the mineral-dust level (hazard/control period: a week). It seemed that mineral-dust level above 0.02 mg/m³ raised the risk of hospitalization and we conducted a conditional logistic analysis excluding cases/controls with mineral-dust level above 0.08 mg/m³, to investigate if lower-level mineral-dust (0.02 mg/m³ to 0.08 mg/m³, which was observed on about 25% days during the study period) raises the risk, compared with the mineral-dust

level less than 0.02 mg/m³. The odds ratio of mineral-dust level 0.02-0.08 mg/m³ for hospitalization was 1.31 (95% CI: 1.07-1.60, p= 0.0097).

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ONLINE FIGURE LEGENDS

Figure E1 Location of Toyama prefecture, Japan and representative distributions of Asian dust on May. 5 2010 forecasted by Chemical weather FORecasting System (CFORS)

CFORS calculates the distributions numerically with CPU-cluster utilizing information about atmospheric conditions, land surface usage, and emission inventories.

Figure E2 Locations of LIDAR and the eight hospitals in Toyama

Figure E3 Representative Moderate Resolution Imaging Spectroradiometer (MODIS) image on Mar. 21, 2002

Figure E4 Crude odds ratios for the relationship between asthma hospitalizations and heavy dust events defined by suspended particulate matter (daily average level above 0.1 mg/m^3 of suspended particulate matter) on the day of the admission (lag 0) or the previous 1-7 days (lag 0-1 to lag 0-7) Error bars represent 95% CIs.

Figure E5A Crude odds ratios of heavy-dust-event for asthma hospitalizations on the day of admission (lag 0) or on the day some days before admission (lag 1 to lag 6), that is, by non-cumulative lag structure. Error bars represent 95% CIs.

Figure E5B Crude odds ratios of heavy-dust-event for asthma hospitalizations on the day of admission (lag 0) or on the day some days before admission (lag 1 to lag 6) in each sex group.

Error bars represent 95% CIs.

Figure E5C Crude odds ratios of heavy-dust-event for asthma hospitalizations on the day of admission (lag 0) or on the day some days before admission (lag 1 to lag 6) in each age group.

Error bars represent 95% CIs.

Figure E6 Crude odds ratios for asthma hospitalizations with various cut-off values in exposure-status of mineral-dust particle level on any day during the previous week of admission

Error bars represent 95% CIs.

Table E1 Correlations between each pollutants and climatic factors

	Mineral dust	Non-M. dust	Pollen	Gaseous NO ₂	Gaseous SO ₂	Gaseous Ox
Mineral dust	1	0.014	0.168	0.013	0.241	0.189
Non-mineral d.	0.014	1	-0.078	-0.149	0.052	0.046
Pollen	0.168	-0.078	1	0.013	0.082	0.002
Gaseous NO ₂	0.013	-0.149	0.013	1	-0.357	-0.672
Gaseous SO ₂	0.241	0.052	0.082	0.357	1	-0.018
Gaseous Ox	0.189	0.046	0.002	-0.672	-0.018	1
Ave. Temp	0.310	0.050	0.217	-0.038	0.166	0.466
Air pressure	-0.055	-0.024	0.035	0.249	0.080	-0.367
Air Pre. Diff.	0.036	0.058	-0.006	-0.189	-0.155	0.029
Humidity	-0.280	0.125	-0.280	-0.082	-0.315	-0.305

Non-M dust; non-mineral dust, Ave. Temp; average temperature, Air Pre Diff.; air pressure difference from the previous day

Table E2 Crude odds ratio of each climatic variables for asthma hospitalization

	Odds ratio	(95%CI)	p value
Temperature on the day (°C)	0.992	(0.973-1.012)	0.429
Temperature on the previous day (°C)	0.979	(0.959-0.999)	0.035
Temp. diff. within the day (°C)	1.014	(0.989-1.039)	0.279
Humidity on the day (%)	0.994	(0.987-1.001)	0.087
Humidity on the previous day (%)	0.992	(0.985-0.999)	0.028
Wind speed on the day (m/s)	0.987	(0.953-1.022)	0.446
Air pressure on the day (hPa)	1.006	(0.9923-1.020)	0.382
Air press. diff. from previous day (hPa)	0.987	(0.973-1.001)	0.074

Definition of abbreviations: CI = confidence interval, Temp. diff. = temperature difference, Air press. diff. = air pressure difference

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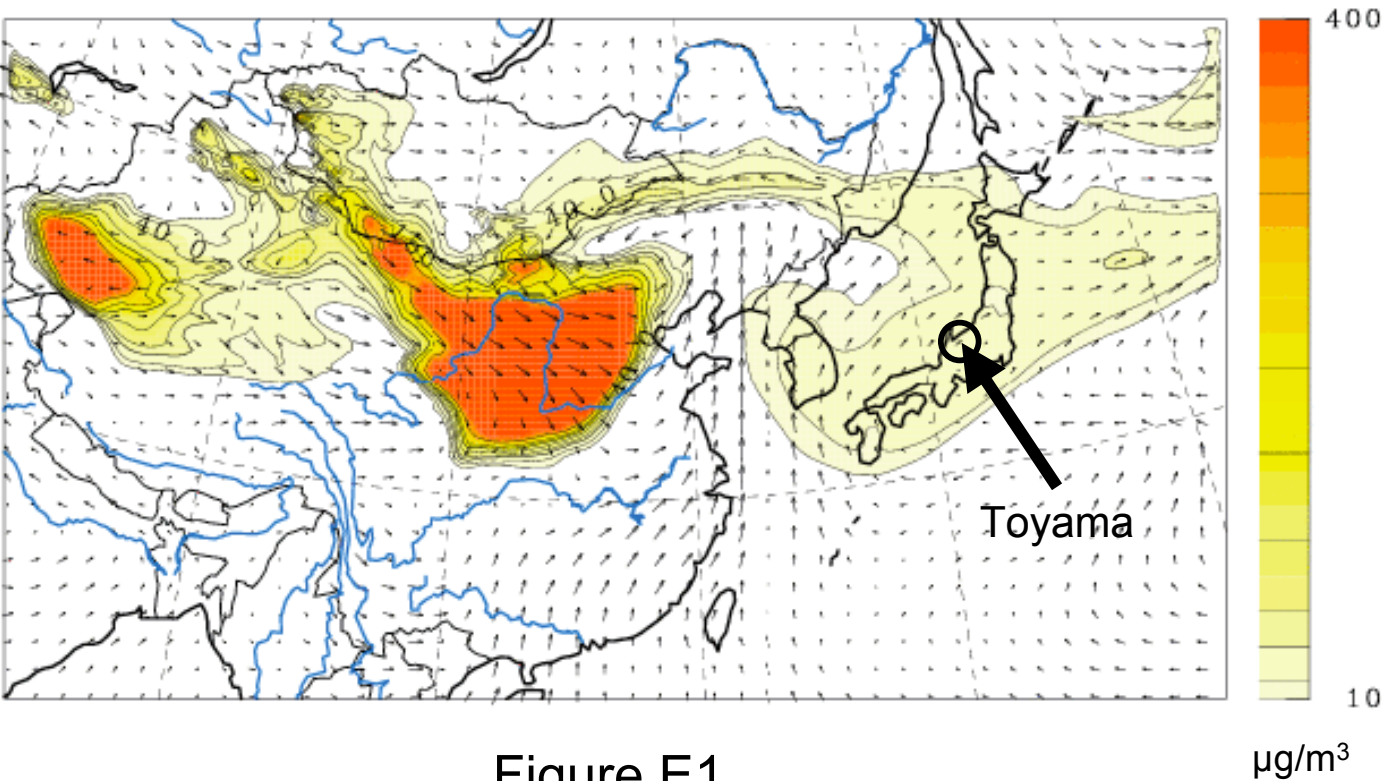


Figure E1

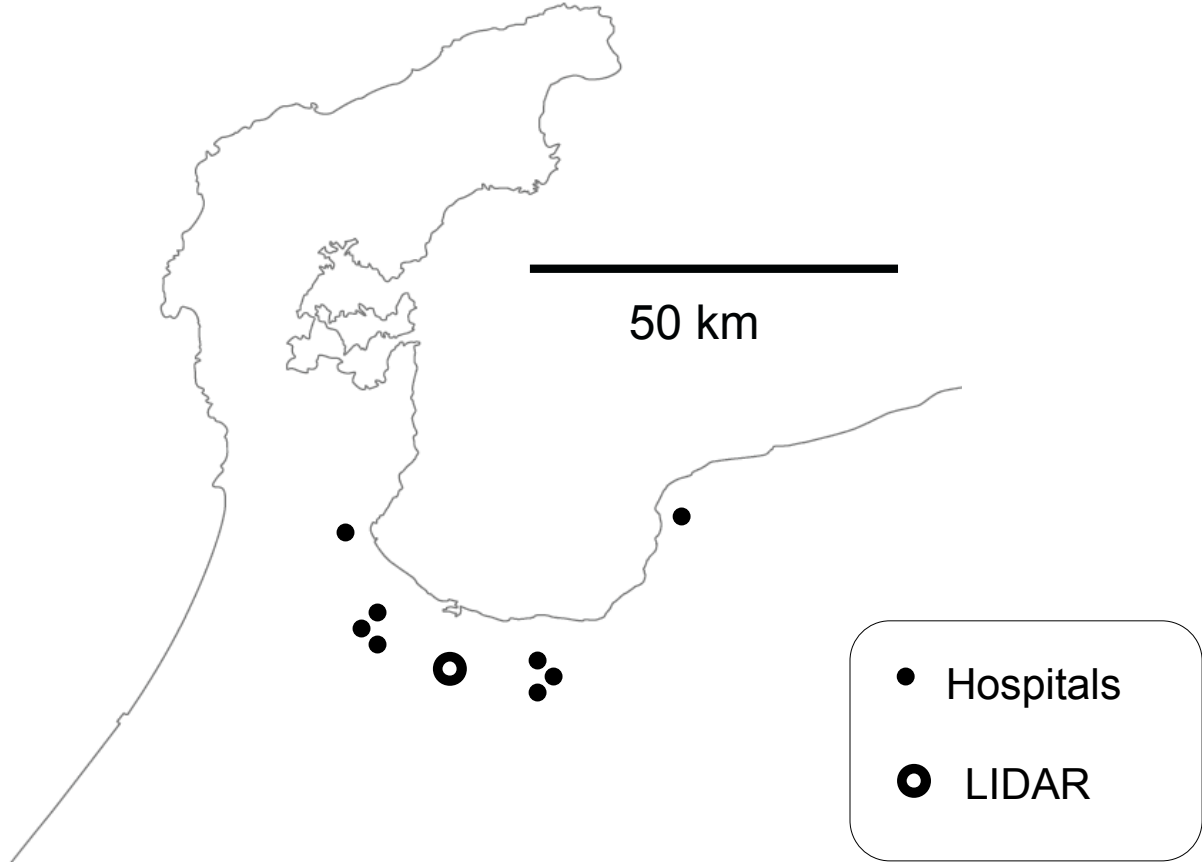


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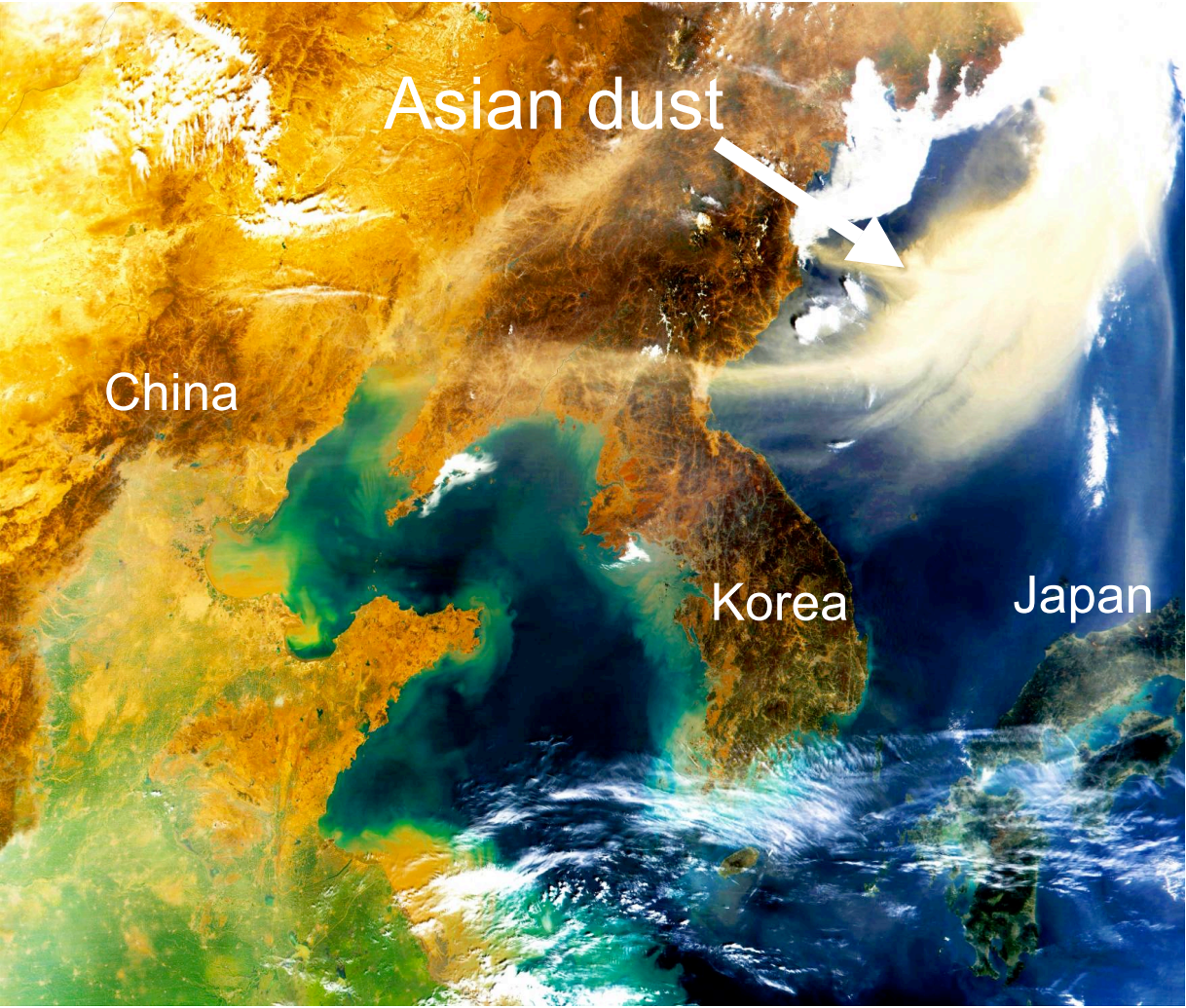


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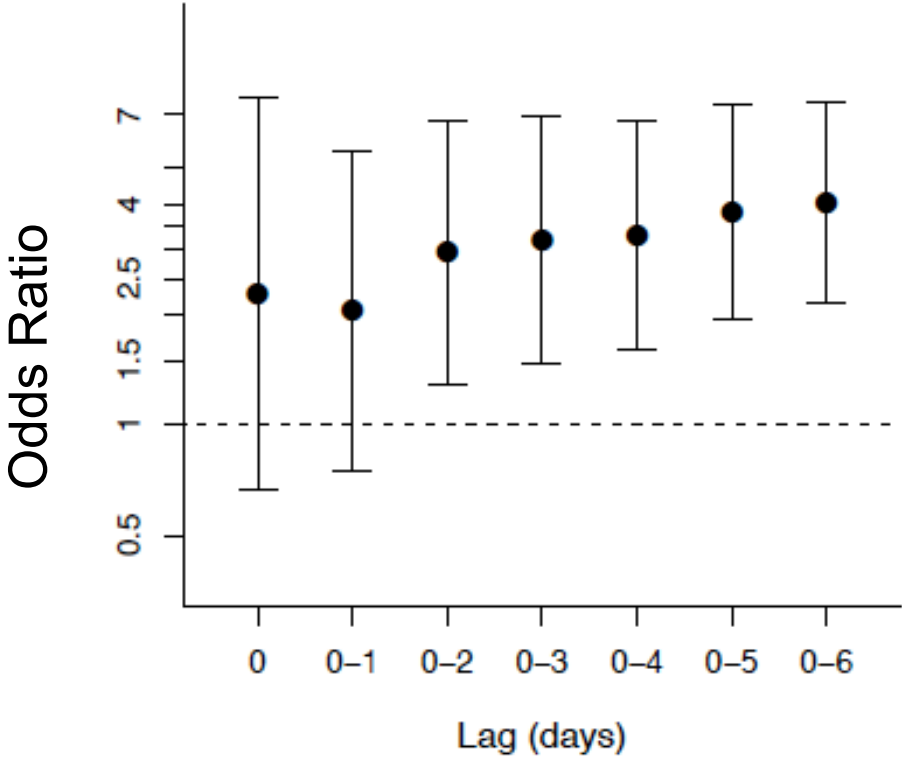


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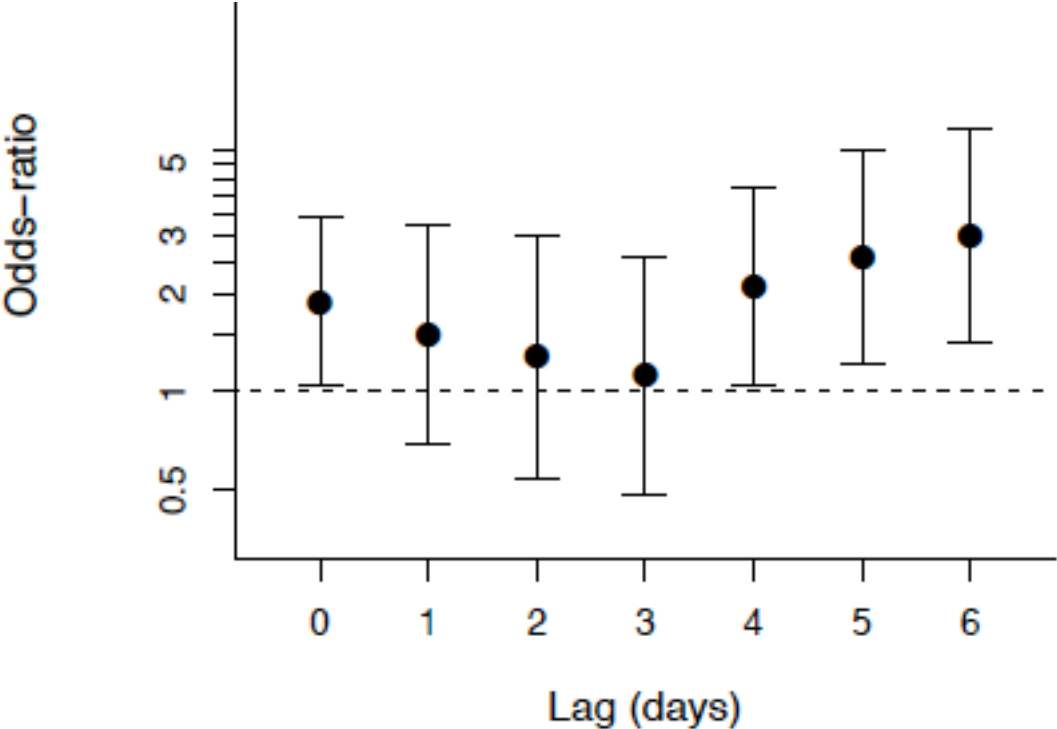


Figure E5A

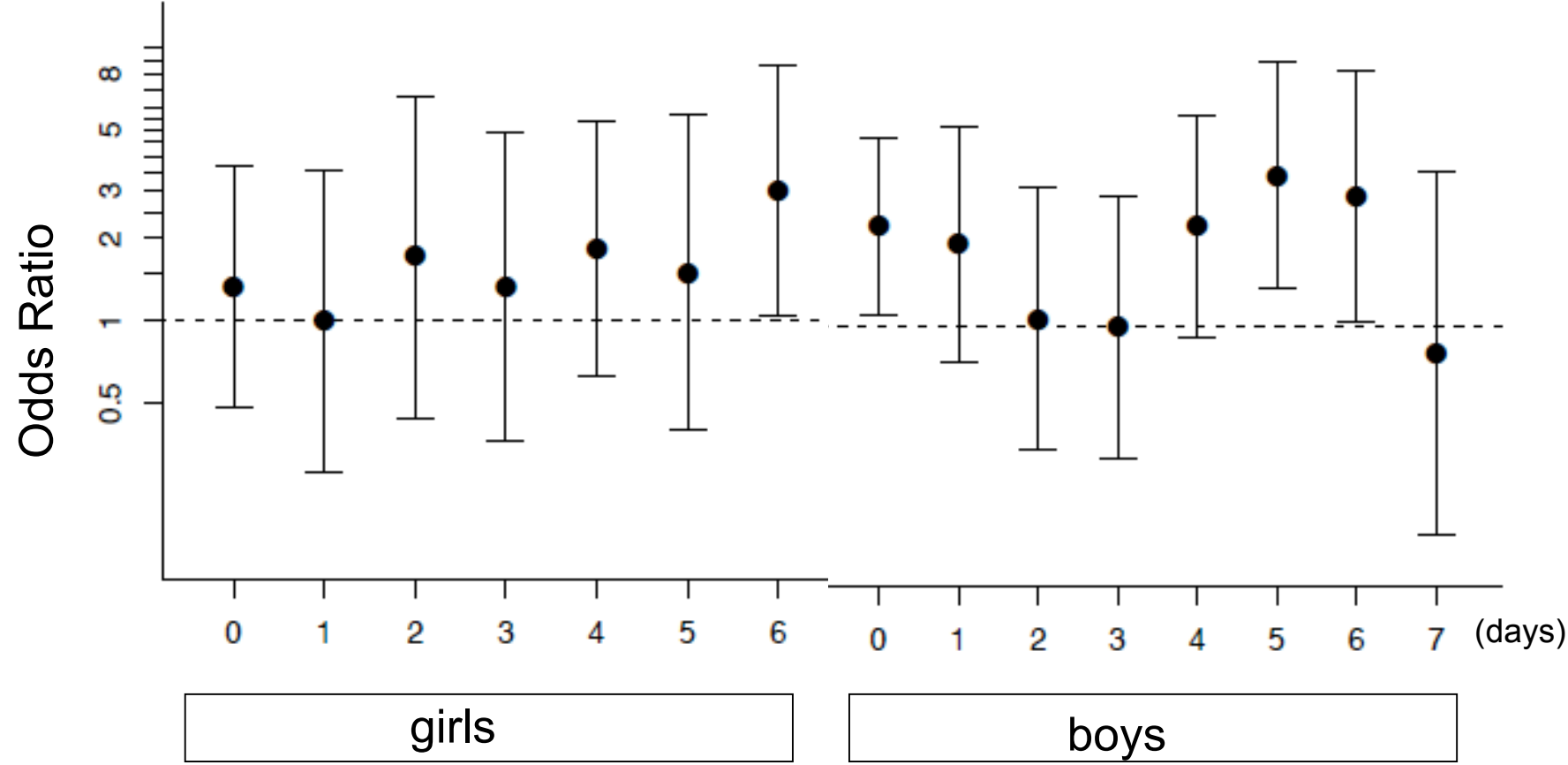


Figure E5B

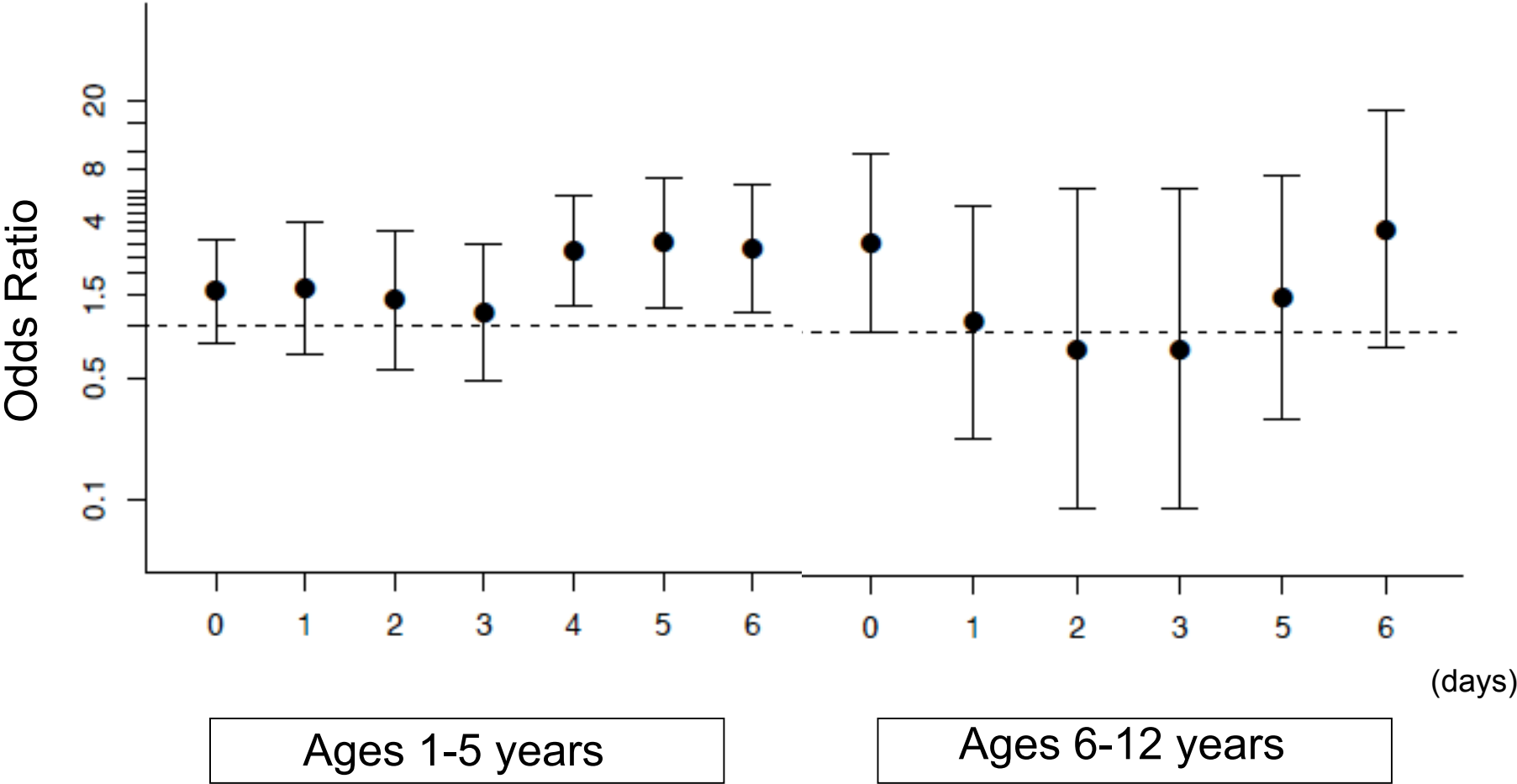


Figure E5C

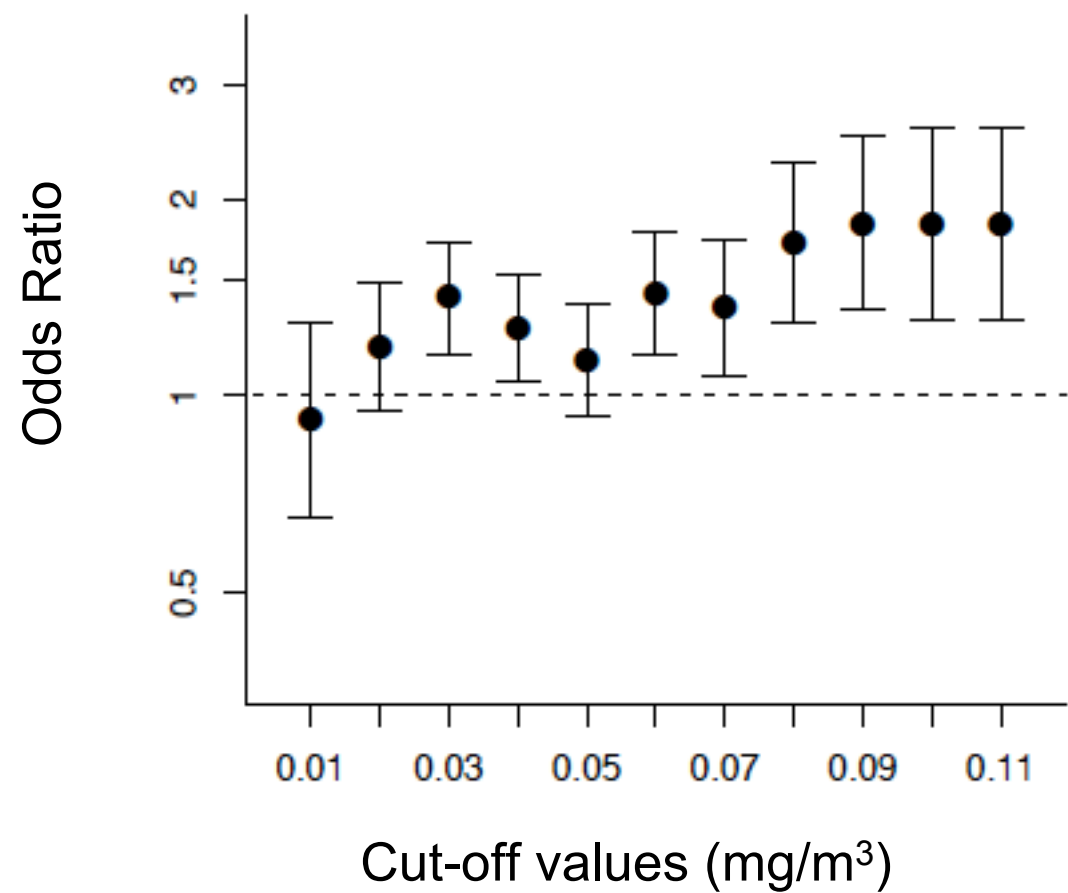


Figure E6